Surgical Operation in Hemophilia B

Use of Factor IX Concentrate

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■ *A concentrate containing plasma clotting factors II, VII, IX and X was used to secure hemostasis for a herniorrhaphy, an osteotomy of a femur, a cup arthroplasty of a hip, and a tonsillectomy in patients with factor IX deficiency. After single infusions of concentrate, the net increase in plasma factor IX activity was 0.7 to 1.0 percent for each in-vitro unit of factor IX infused per kilogram of body weight. After large infusions of concentrate in two patients, the disappearance pattern of factor IX had two phases: a first component with half-disappearance times of 4.4 and 6 hours, and a second component with half-disappearance times of 26 and 32.6 hours.*

THE RECENT DEVELOPMENT of a concentrate containing plasma clotting factors II, VII, IX and X has provided the means to achieve good hemostasis in deficient patients, and to study the kinetics of the distribution and disappearance of those factors.[1] Observations on three patients with factor IX deficiency who received the new concentrate for surgical procedures are described below.

Methods

Administration of Concentrate

One lot of concentrate* was used for all patients, with the exception of two doses from a second lot given in the postoperative period to the patient in Case 3, and the concentrate used for the second operation in Case 1. Each vial of lyophilized concentrate contained 500 units of factor IX activity, as measured in vitro by the manufacturer. One unit of factor IX activity is defined as that amount found in one milliliter of fresh average normal plasma. Immediately before use, each vial was reconstituted with 20 ml of sterile water. Administration was by intravenous drip at the rate of 10 to 15 ml per minute.

Coagulation testing

Blood specimens were mixed in a proportion of 9:1 with an anticoagulant consisting of two parts 0.1 molar citric acid and three parts 0.1 molar sodium citrate, and were centrifuged at 12,100 g at 4° C. for 20 minutes. Plastic syringes, tubes and pipettes were used. The plasma aliquots were stored at —30° C. for up to one week before testing.

Factor IX was measured by a one-stage activated partial thromboplastin time method, as described by Schiffman and coworkers.[2] Factor II

*Konyne®, prepared by Cutter Laboratories, Berkeley, California.

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was measured by the method of Hjort et al,[3] modified by the addition of Hjort's proconvertin reagent to provide excess factor X. The test for factor IX inhibitor was performed by incubating equal parts of normal plasma and patient plasma at room temperature and comparing the factor IX activity of the mixture at two hours to that at zero time; normally, no factor IX activity is lost.

Blood specimens were drawn immediately before and 15 minutes after administration of concentrate. For the determination of the disappearance pattern of factor IX, specimens were drawn at intervals during several days after the administration of a single large dose of concentrate. For the calculation of the disappearance curve, as described by Hoag et al,[1] the patients' inherent factor IX levels were subtracted from all the post-infusion values. Each disappearance curve appeared to have two exponential components. A regression line was fitted to the second component by the method of least squares, and extrapolated to zero time. The amount of factor IX accounted for by the second component was subtracted from the observed values for the first component, and a regression line was fitted to the resulting values for the first component. The ratio of the second component at zero time to the total concentration at zero time is assumed to measure the apparent volume of distribution. The point at which the curve fitted to the observed values joins the calculated line of the second component is said to be the equilibration time.

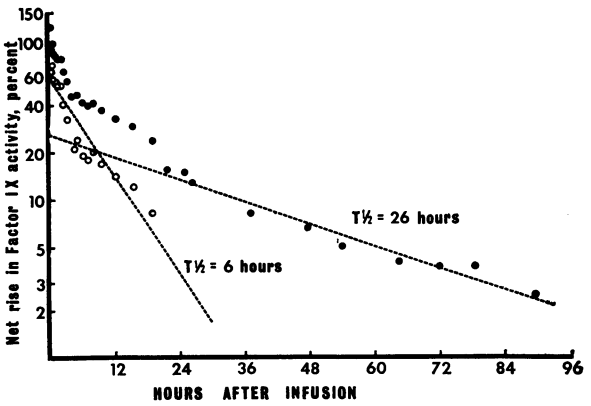

Chart 1.—Disappearance pattern of factor IX after infusion of 280 ml of concentrate (7,000 in-vitro factor IX units) in a 61-kilogram patient (Case 1) with severe hemophilia B. Closed circles represent observed values, and open circles calculated values for the first component. (T½ = Half-disappearance time.)

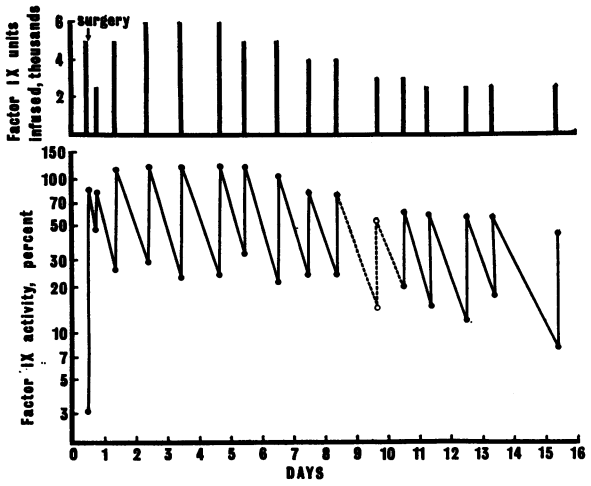

Chart 2.—Infusions of factor IX concentrate and plasma factor IX activity in a 61-kilogram patient (Case 1) with severe hemophilia B during and after osteotomy of the femur. Closed circles and solid lines represent observed values, open circles and dotted lines represent estimated values.

Studies of Patients

Case 1. The patient was a 29-year-old man weighing 61.4 kg with severe hemophilia B, factor IX activity 0.7 percent. He had had hemarthrosis frequently and in the preceding three years had fractured his left femoral condyles on three occasions. A pronounced valgus deformity of the left leg had resulted, and on the right side there were advanced arthritic changes of the hip joint, causing constant pain. In November, 1968, a patellectomy, osteotomy of the distal left femur and reconstruction of the left knee were performed. Estimated blood loss was 500 ml and wound healing was normal. Four days before the operation, concentrate containing 7,000 factor IX units was administered, and frequent blood specimens were drawn for the disappearance study (Chart 1). Concentrate containing 5,000 factor IX units was infused just before the operation. Infusions of 5,000 to 6,000 units of factor IX were given daily the first week after the operation, and 2,500 to 4,000 units daily the second week (Chart 2). The patient then was given 500 ml of lyophilized pooled plasma each week day before physical therapy sessions for another two months. In January, 1970, a cup arthroplasty of the right hip was performed. Estimated blood loss was 1,100 ml and wound healing was normal. Concentrate containing 6,000 factor IX units was given before the operation, and 4,000 factor IX units on each postoperative day for two weeks.

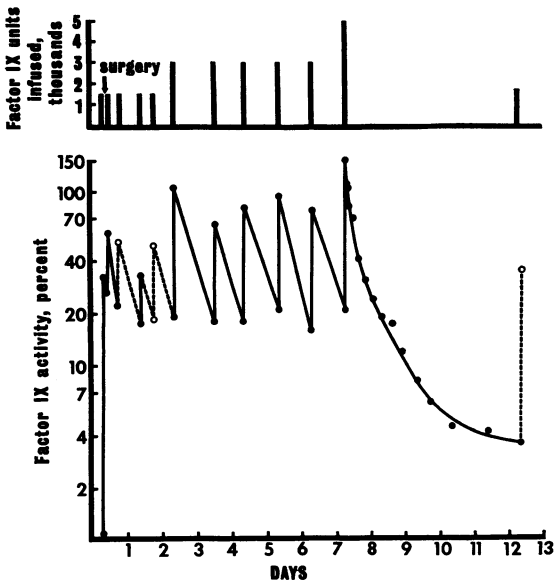

Chart 3.—Infusions of factor IX concentrate and plasma factor IX activity in a 33-kilogram patient (Case 2) with severe hemophilia B during and after a herniorrhaphy. Closed circles and solid lines represent observed values, open circles and dotted lines represent estimated values.

Case 2. The patient was an 8-year-old boy weighing 33 kg with severe hemophilia B, factor IX activity 1.1 percent. In August, 1968, an elective repair of a left indirect inguinal hernia with incarcerated omentum was performed. Blood loss was nil and wound healing was normal. Concentrate containing 3,000 factor IX units was administered before and during the operation, and another 3,000 units were given on each of the first seven postoperative days (Chart 3). Concentrate containing 5,000 factor IX units was given on the seventh postoperative day and multiple blood specimens were taken over the next five days for the disappearance study (Chart 4). Concentrate containing 1,500 factor IX units was then given and he was discharged. He has remained well.

Case 3. The patient was a 14-year-old girl, weighing 50 kg, with 22 percent factor IX activity. Her two brothers and other male relatives had severe hemophilia B, and presumably she was a carrier. She had required plasma infusions on occasion to treat excessive menstrual bleeding, epistaxes and bleeding from infected tonsils. She was given concentrate containing 2,000 factor IX units immediately before tonsillectomy in January, 1969, and 500 factor IX units daily for seven days thereafter. For seven more days she received 500 ml of lyophilized pooled plasma per day. Operative blood loss was minimal and wound healing was normal.

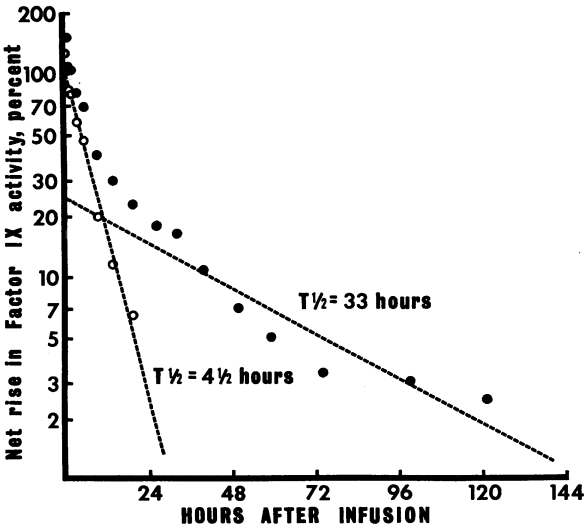

Chart 4.—Disappearance pattern of factor IX after infusion of 200 ml of concentrate (5,000 in-vitro factor IX units) in a 33-kilogram patient (Case 2) with severe hemophilia B. Closed circles represent observed values, and open circles calculated values for the first component. ($T\frac{1}{2}$ = Half-disappearance time.)

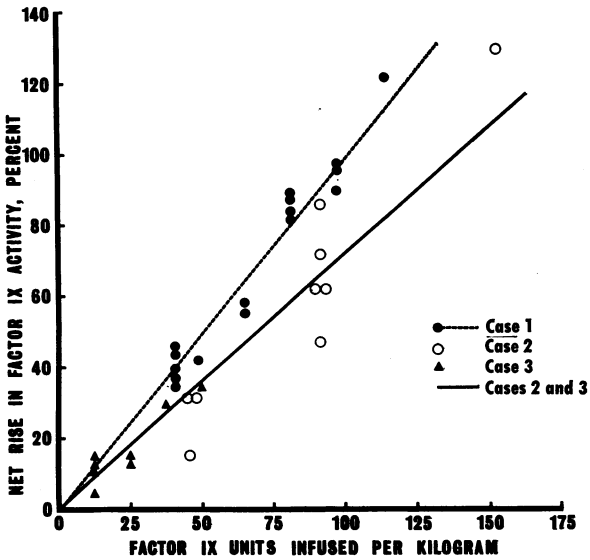

Chart 5.—The factor IX activity recovered in vivo 15 minutes after infusions of concentrate is related to the number of factor IX units infused, as measured in vitro.

Results

After single infusions of concentrate in Case 1, the immediate net increase in plasma factor IX activity was approximately 1 percent for each in-vitro unit of factor IX infused per kilogram of body weight. In the other two cases a smaller rise, approximately 0.7 percent of factor IX activity for each in-vitro unit of factor IX infused per kilogram, was observed (Chart 5).

The plasma factor IX activity of the patient in Case 1 was raised to 122.5 percent at the beginning of the disappearance study. The distribution of factor IX activity levels obtained was compatible with a two-component disappearance, with the first component having a half-disappearance time of 6 hours, and the second component 26 hours (Chart 1). The equilibration time was approximately 22 hours, and the apparent volume of distribution was 2.8 times the plasma volume. The observed values also suggest the possibility of a three-component pattern, having an initial component with a rapid half-disapperance time—0.6 hours—a second component with 10.4 hours, and a final component with 26 hours.

The plasma factor IX activity of the patient in Case 2 was raised to 151 percent at the beginning of the disappearance study. The distribution of values suggested a two-component disappearance, with the first component having a half-time of 4.4 hours and the second component 32.6 hours. The equilibration time was approximately 24 hours and the apparent volume of distribution was five times the plasma volume.

The plasma factor II activity of that patient before the first infusion of concentrate was 108 percent. On the seventh postoperative day, before the large infusion of concentrate, the factor II activity of his plasma was 320 percent. Immediately after the large infusion it rose to 840 percent; at 13 hours it was 410 percent, at 25 hours 270 percent, and at 121 hours 175 percent.

Adequate hemostasis during the operations was obtained with initial factor IX activity levels of 32.5 percent in Case 2, of 85.5 and 121 percent in Case 1 and 57 percent in Case 3. No postoperative bleeding occurred. The patient in Case 2 received daily concentrate for a week and had minimum factor IX activity levels of 16 to 21 percent. In Case 1 concentrate was given daily for two weeks on both occasions, and the patient had minimum factor IX activities of 12 to 33 percent after the first operation and 20 to 35 percent after the second. The patient in Case 3 had minimum factor IX activities of 35.5 to 38.5 percent during the week of daily concentrate therapy.

The vital signs remained stable during the infusions of concentrate in all patients. No symptoms of allergic sensitivity appeared. There were no clinical signs of hepatitis during the ensuing months. Factor IX inhibitors could not be detected before the initial infusions or after the final ones.

Discussion

The recovery of factor IX activity in the plasma of patients in the present report was less than would be predicted from calculations based on the patients' estimated plasma volumes and the factor IX activity of the concentrate, measured in vitro. Hoag et al,[1] using the same concentrate, recovered almost half as much factor IX activity in vivo as was predicted; the recovery in Case 1 in the present report was almost half that expected. Less than half the expected activity was recovered in vivo in the other two patients—results that are comparable to the best recoveries reported by Gilchrist et al,[4] who used a different factor IX concentrate. The discrepancy between the factor IX units measured in vitro (and stated on the label of the concentrate) and the in-vivo factor IX activity recovered in the patient is confusing to medical personnel accustomed to the close correlation between in-vitro factor VIII units administered in the form of factor VIII concentrate, and the factor VIII recovered in the patients who receive it. If a physician did not read the suggestions on dosage given on the package insert of the factor IX concentrate, and instead calculated dosage by the same formula he used for factor VIII concentrate in hemophilia A, he would administer half as much factor IX concentrate as would really be needed to achieve a desired factor IX activity in his patient's plasma.

Hoag et al described mean half-disappearance times of 4.6 $\pm$ 1.6 hours for the first component and 31.5 $\pm$ 9.1 hours for the second. The half-disappearance times found in the three patients herein described were within one standard deviation of their values. The equilibration times were also similar. The apparent volume of distribution in Case 1, 2.8 times the plasma volume, is similar to their mean value to 2.7 $\pm$ 0.4 times the plasma volumes. The patient in Case 2 had a much higher value of five times the plasma volume. The reason for the difference is not clear. In Case 2 the patient was given a much higher plasma factor IX activity at the start of the disappearance study than most of the patients reported by Hoag et al, and he was recovering from an operation, whereas the patient in Case 1 was not. Hoag et al found no difference in the disappearance patterns between actively

bleeding and nonbleeding subjects, although a febrile patient had a more rapid disappearance than the nonfebrile.

The minimum factor IX activity levels at which surgical hemostasis and postoperative healing can confidently be expected have not been established. Loeliger et al[5] maintained factor IX levels at a minimum of about 30 percent for a week in two patients who had operations for talipes equinus. Hoag et al maintained minimum levels of 15 percent in the postoperative period in two patients. I presumed that a level of factor IX activity well above 30 percent on the day of operation, while the initial clots were being formed, would be advisable. I had known a carrier of hemophilia B with 33 percent factor IX activity who bled for several days following tonsillectomy, so I felt obligated to maintain factor IX levels well above 30 percent in the patient in Case 3 while she recovered from tonsillectomy. For uneventful recovery from the other procedures, minimum levels—as low as 12 and 16 percent factor IX activity—appeared to be adequate. A once-daily schedule of concentrate administration proved to be convenient and practical, although a twice-daily schedule of administration with the same total daily dose would be expected to provide a slightly higher minimum factor IX activity. Further experience with surgical operations on patients deficient in factor IX is needed before secure recommendations about minimal hemostatic factor IX levels can be made.

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ANESTHESIA IN BURNED CHILDREN

"In our series of 282 children with burns, we had one whose heart slowed at anesthesia; no cardiac arrests; and no deaths in the operating room or recovery room. I think this can be attributed first to good anesthesiologists; but I think there are several other points of importance. One is the maintenance of temperature with a warm-water mattress; another is transfusions preoperatively to provide a good patient. We have also found that 'prepping' the patient in the tank has been a great help. We send the patient to the Hubbard tank, have him bathed, cleaned, and then wrapped in aluminum foil and brought to the operating room where very little time is necessary for 'prepping.' . . . We've also tended to work one side of the body, to work out a plan that allows us to use donor and recipient areas on the same side, if possible. We also limit ourselves to about 30 to 60 minutes. We give our anesthesiologists the dictatorial control of a TV producer to tell us to stop."

—EDWIN IDE SMITH, M.D., Oklahoma City

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